A breath of fear : a translational approach into the mechanisms of panic

Individual and socio-economic relevance

Panic disorder (PD) is a prevalent condition that affects about 4% of the general adult population (Weissman et al., 1997). The recurrent, unexpected nature of its core feature, panic attacks (PAs), is highly frightening and stressful for patients. Before PD is being diagnosed, patients typically associate the symptoms (e.g., shortness of breath, choking, dizziness, chest pain, palpitations) with heart attacks and seek help in emergency departments (Fleet et al., 1996), without receiving a solid explanation for their problem. Over time, patients often develop concerns about future attacks and eventually avoid places and situations, in which previous attacks occurred, in which it may be difficult to get help (e.g., being outside alone) or in which a PA might be embarrassing (e.g., in a restaurant). Consequently, patients are often confined to their homes, unable to participate in social activities or to go to work, leading to financial problems for the patient as well as the employer and a marked decrease in quality of life (Davidoff et al., 2012; Mendlowicz and Stein, 2000). In addition, available treatments are associated with many side effects (Batelaan et al., 2012) and relapse rates are high (Craske and Zucker, 2001). Therefore, the costs associated with an individual with PD are substantial in terms of medical care and decreased productivity such as missed working days. At the population level, the annual societal costs of €226 million equal the range of the combined costs of general anxiety disorder, social phobia, and simple phobia (Batelaan et al., 2007).

Refining the diagnosis of PD

As the symptoms of a PA such as chest pain and breathing difficulties closely resemble those of a heart attack or acute asthma, patients commonly seek help at emergency or heart departments (Fleet et al., 1996). Often costly tests such as angiography are performed (Zaubler and Katon, 1998), however without finding a medical explanation. In fact, up to 25% of patients with chest pain and visiting hospital emergency departments have been shown to fulfil the diagnostic criteria of PD (Huffman and Pollack, 2003). This observation emphasizes the need for a better and fast diagnosis of PD, which to date is based on self-reports during clinical interviews. It is evident that the presence and intensity of emotions (e.g., fear of dying) and some symptoms such as dizziness experienced during a PA can only be evaluated by the individual itself. However, PAs are also accompanied by marked physiological symptoms. Therefore, in the first study of this thesis, we went beyond the traditional approaches and included physiological measurements to complement self-reports. We showed that in healthy subjects particularly the diastolic blood pressure was a sensitive parameter that reflected the degree of self-reported emotions and panic symptoms, and might therefore represent a suitable biomarker. The next conceptual steps are to confirm the potential of the diastolic blood pressure as biomarker in PD patients

and, when validated, incorporation in the daily clinic. When no heart- or asthma-related explanation can be found, patients could take a vital capacity breath of CO_2, whilst blood pressure is measured. The combination of a high emotional response and assessing the diastolic blood pressure could support the clinical diagnosis. The incorporation in the clinic is relatively easy in terms of methodology: blood pressure can be measured using a non-disturbing finger cuff connected to a cardiovascular monitor. Such devices are commercially available and costs are relatively low. To disseminate this application, we published the study addressing the inclusion of physiological measurements to complement self-reports in an international peer-reviewed journal and present the results in lectures and at (inter)national conferences for scientists. In addition, we work together with national health centers to inform clinicians about the potential use. In the mid-term, including the diastolic blood pressure might be a highly value addition for diagnosing PD and providing the patients the right medical explanation and treatment.

Improving current pharmacological treatments in PD and other disorders

In PD, the two main treatment options are pharmacotherapy and cognitive behavioral therapy. Despite that the current pharmacological drugs are effective in general, many patients remain symptomatic or do not respond to the first-line choice of treatment (Baldwin et al., 2014). In addition, the many side effects such as sexual dysfunction, weight gain, sleeplessness, and nausea (Cascade et al., 2009) often lead to a low acceptability of the drug by the patient. After drug discontinuation relapse rates are high, with up to 70% (Craske and Zucker, 2001). Therefore, to improve the current treatment options and to find new neurobiological targets, it is important to make progress in gaining more insights into the molecular mechanisms underlying PAs. Human experimental models are limited in their potential to investigate molecular mechanisms. However, in contrast to the long-standing use of panic-provoking agents such as CO_2 inhalation in humans, relatively little research has been done in rodents in the direct framework of PD. In addition, human panic provocation studies rely on self-reports, while in rodent studies the main outcome parameter is the animal's behavior, two outcomes that are difficult to compare. This divergence between human and animal models hampers the translation of the results and is one of the reasons why drugs that proved to be promising in animals frequently fail in the clinical phase.

To optimally compare the aspects of human and animal research, it is important to perform experiments and use outcome measures that are as similar as possible. Although some studies already applied CO_2 exposure to rodents as experimental stimulus, the field would greatly benefit from adding outcome variables that can be obtained in both research domains, for instance cardio-respiratory parameters, as we did in the present

thesis. When using the same stimulus and outcome measures in both species, the likelihood of obtaining an effective drug in humans based on a promising compound in the rodent model strongly increases. In addition, given the spectrum of CO_2-reactivity and to reduce the burden for patients with PD, the potency of new therapeutics can be evaluated in healthy subjects and then followed by first-degree relatives of PD patients, who show an intermediate vulnerability to CO_2 when compared to healthy participants and PD patients. Eventually promising drugs can be tested in patients, in collaboration with pharmaceutical companies. Given that the pathophysiology of PD is not yet fully understood, more research is needed and potential molecular targets have to be studied in detail in order to have value for patients in the future. In the present thesis, we further put forward pH-sensitive ion channels as promising candidates. Future studies could elucidate the effects of, for instance, drugs selectively inhibiting those channels. Starting in rodents, with making use of a combined behavioral-physiological approach established in the course of this PhD project, and extending to humans might lead to better treatment strategies in the mid-term.

Despite that the focus in the present thesis is on PD, going beyond the commonly used methods is likely to be highly beneficial for all research disciplines, in which data from rodent research are applied in humans and in which drug development is involved. More effective drugs and with less side effects, and decreasing the time to test them is of pivotal importance for patients to return to a normal daily life, which also has a large impact on society and economics.

CO_2 inhalation in exposure therapy in PD

A further application of the results of the present thesis may be in light of exposure therapy in PD, a form of cognitive behavioral therapy. Exposure therapy is based on the repeated exposure to the frightened stimulus until patients have learned that there are no life-threatening consequences, associated with a reduction in discomfort to a tolerable level that does not hamper daily life anymore. In case of PAs, the arousing bodily sensations are provoked by, for instance, intentional hyperventilation (Meuret et al., 2005), spinning in a chair, and running on the spot (Ito et al., 2001). However, only a fraction of the symptoms of a full-blown PA are provoked using these approaches (Antony et al., 2006; Lee et al., 2006). In contrast, CO_2 inhalation triggers the fear and bodily response resembling naturally occurring PAs. The response to a few CO_2 inhalations is relatively consistent (Coryell and Arndt, 1999; Verburg et al., 1998), but repeated exposures were shown to cause desensitization to some extent (Beck et al., 1997; van den Hout et al., 1987). Therefore, 35% CO_2 is a promising tool for exposure therapy in patients with PD. It is commonly used in the daily practice at the Academic Anxiety Hospital, Maastricht, and

receives modest interest from other centers as well. To become an addition or alternative to pharmacological treatment that is frequently accompanied by considerable side effects (Cascade et al., 2009), it has to be investigated how many inhalations are required to obtain relevant effects in PD patients. Patients can be recruited in the clinical setting when seeking treatment. By systematically assessing the required number and frequency of CO_2 exposure sessions, application guidelines can be provided to clinicians in a few years. Clinicians can be reached via national health centers and large conference such as the annual meeting of the American Psychiatric Association (APA) and the European College of Neuropsychopharmacology (ECNP).

To date, it is largely unknown what the biological basis of exposure therapy is, as is the case regarding the observed desensitization to repeated CO_2 exposure. To further elucidate the involved mechanisms, monitoring the physiological response in terms of respiratory and cardiovascular parameters, as we did in the studies presented in this thesis, represents an easy to implement and relatively inexpensive starting point. Thereby, we could obtain insights in whether the effects of CO_2 exposure therapy are associated with personal perception or also with physiological alterations. The relevance in this regard is twofold: First, to potentially offer an add-on therapy if changes on the physiological level are essential for relevant effects or exert an additional beneficial effect. This could be in form of, for instance, relaxation or breathing training in patients. Second, to possibly identify patients at risk for relapse in order to intervene in time by, for instance, scheduling earlier appointments with the clinician. Furthermore, in the future, the effects of CO_2 exposure therapy might also be boosted by augmentation with pharmacological drugs. To test the therapeutic potential of drugs, a combination of repeated CO_2 exposure and assessing the behavioral as well as physiological response could be tested in rodents. In addition, animal research might also reveal new neurobiological targets. Overall, there is a high potential of CO_2 inhalations in the framework of treatment options for PD, however much research has still to be done before clinical applications can be expected.

Decreasing the stigmatization in mental disorders

Despite that mental disorders are highly prevalent, the field of psychiatry is still perceived as having a negative connotation. Patients have a double burden, suffering from severe symptoms of the illness and experiencing stigmatizing attitudes from society. Patients are often negatively judged by other people as being dangerous (Whalen, 2006) or crazy. These beliefs lead to discrimination, avoidance, and reluctance to provide support and help. It is apparent that this additionally affects the patients' life in a negative manner, on an emotional level as well as in terms of daily life activities and willingness to seek treatment at psychiatry wards (Prasko et al., 2011; Whalen, 2006). Frequently, patients

start to internalize believes of their environment, stigmatize themselves, and loose self-esteem and confidence into the future (Corrigan and Watson, 2002).

In contrast to the belief that mental disorders are due to a weak character (Corrigan and Watson, 2002), there is a large body of scientific evidence that mental disorders have a biological origin in form of vulnerability factors that interact with environmental factors. The present thesis contributes to extending our understanding of PD by showing that, for instance, genetic variants are associated with a heightened reactivity in an experimental model of PAs. By raising awareness for a biological basis of mental disorders, de-stigmatization could be achieved. Target groups include the community residents, patients, relatives, and health insurances that often reimburse treatment of psychiatric disorders to a smaller extent than of physical illnesses. Performing educational campaigns, in collaboration with health care providers, patient organizations, and the media, could provide information to a broad audience and clarify misunderstandings based on scientific evidence. In addition, it has been shown that interpersonal contact with patients is associated with less stigmatization (Corrigan and Watson, 2002). Therefore, it is important to actively involve patients in activities, for instance in discussion meetings, in which they tell about their personal experiences. Moreover, education should start early, for instance at school, as it was shown that young adults with an age of 16-19 years are more likely to have negative attitudes towards mental disorders than older people (Crisp et al., 2005). This could significantly increase the patients' quality of life and give them a more positive future.

Conclusion

The present thesis went beyond the commonly used methods by using a unique approach in psychiatric research to date, thereby providing promising opportunities for future thriving applications in the framework of PD as well as mental disorders in general. Multi-disciplinary scientific collaborations and interacting with various stakeholders may accelerate the endeavors of science to positively impact on patients' lives, which, in turn, could reduce the socioeconomic costs related to mental disorders. Money saved could then be spent on research again to further push forward discoveries in the same or other disciplines, to disseminate applications, and to decrease stigmatization by doing campaigns. Thereby, we may be able to make a significant step towards bringing together science, society, and clinic, and to perform research that benefits the patient in the short-term.

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